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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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ROPES & GRAY LLP
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 01/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/332,866	LEVEUGLE ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14,15,17,20,21 and 28-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14,15,17,20,21 and 28-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on **10/06/03** has been entered.

Applicant adds new claims 35-41 which are related to claims 14-15,17, 20-21, 28-34 and are not new matter.

Accordingly, claims 14-15,17, 20-21, 28-41 are being examined.

The submission of the Declaration of Dr. B. Schultes is acknowledged and entered.

The following are the remaining rejections.

REJECTION UNDER 35 USC 112, SECOND PARAGRAPH, NEW REJECTION

Claim 39 is indefinite for the use of the language "low dose", which does not set forth the metes and bound to the patent protection desired.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT

Claims 14-15, 17, 20-21, 28-34 remain rejected under 112, first paragraph, pertaining to lack of enablement of a method for inducing an immune response to prostate specific antigen, or an antibody that specifically binds to prostate specific antigen in a patient with prostate cancer, for reasons already of record in paper No:24. New claims 35-41 are rejected for the same reasons already of record.

Applicant argues as follows:

A) Example 12

Applicant argues that in paper No:12, the Examiner stated that this application is enabled for a method of treating prostate cancer, comprising administering antibody AR47.47 which specifically binds to the epitope of amino acids 139-163 of PSA (SEQ ID NO:1) (when claims were drawn to circulating PAS).

Applicant submits a Declaration by Dr. Schultes, stating that the animal model used in Example 12 is not representative of prostate cancer in human, wherein in human prostate cancer, the disease progresses much more slowly timescale. Applicant asserts that thus the protocol of Example 12 is not designed to be predictive of the likehood of success or failure for treating human patients having prostate cancer.

Applicant further asserts that by the administration of the claimed AR47.47 (Ab1), antibody Ab3 equivalent to Ab1 could be expected to be produced via the idiotypic netwok, and antibody Ab3' which recognizes multiple epitopes of PSA could be produced via processing of an immune complex of AR47.47 and PSA.

Applicant argues that it is not relevant that PSA is a self antigen, because the instant application describes a method that breaks tolerance to self antigens. Applicant

further argues that it would have been expected that adequate number of CTLs with high affinity for PSA would be produced.

Applicant further argues that if the claimed antibody AR47.47 could induce anti-idiotypic antibodies against PSA in a cancer free host, the claimed antibody would also be expected to induce anti-idiotypic antibodies against PSA in a host with prostate cancer. Applicant argues that the presence of PSA, produced by prostate cancer, is important for immune complex formation and induction of multiple epitopic anti-PSA antibodies (Ab3') and T cells specific for PSA.

Applicant recites the references by Chapman et al, Herlyn et al, stating that the technology of anti-idiotypic antibodies (Ab3) was well known at the time of filing of the instant application.

B) Example 11

Applicant argues that to prevent relapase, an immunotherapeutic approach using antibody AR47.47 would be very useful. Applicant argues that the mice in Example 11 were administered Ab1 (antibody AR47.47) prior to tumor inoculation to present an adequate model of early human prostate cancer, or human prostate cancer after primary treatment.

C) Experiments 8, 13, 10 and 14 in Example 12

Applicant argues that the Ab1 antibody did not induce a protective immune response in the majority of animals, as indicated by the fact that antibodies titers are not higher in AR47.47 treated mice than in the controls, is likely due to tumor implantation prior to immunization, and insufficient time to immunized the mice appropriately.

Applicant argues that however, complete remission of 100 percent of animal models would not be required to expect that the subject treatment be useful in human patients. Applicant argues that the experimental data indicate that this treatment would be most useful in early stage of disease or as an adjunct treatment after first-line therapy, but would unlikely to be successful in late stage disease.

D) Ab2 correlation with method for inducing an immune response

Applicant argues that it was well known and accepted in the art that administration of Ab1 antibodies induce the formation of Ab2 antibodies, which ultimately induce the formation of Ab3 antibodies. Applicant further asserts that the claimed Ab1 AR47.47 also generates Ab3' antibodies which are induced by complexes of AR47.47 and the tumor antigen, PSA. Applicant asserts that the Ab3' response is a subset of an anti-PSA response wherein the anti-PSA antibodies recognize epitopes distinct from the Ab1 antibody on a multi-epitope antigen such as PSA.

Applicant argues that induction of Ab2 and Ab3 antibodies is routine in the art, and is demonstrated in the specification. Applicant argues that in Example 10, a competitive binding assay demonstrate the presence of both Ab2 and Ab3 antibodies, as also indicated in the competitive assays of Example 7, 9, 11 and 12. Applicant asserts that Ab3 thus were successfully produced, and that one would expect that Ab3 would be produced as a consequence of the anti-idiotypic network.

E) Antibody induction specific for tumor.

Applicant argues that it was well known and accepted in the art that when Ab1 antibodies are administered in a patient, Ab3 are induced in sufficient amount in the

host with tumor burden to elicit an effective immune response, as is set forth in the Schultes Declaration. Applicant further asserts that cancer patients produce PSA, which allows for immune complex formation between AR47.47 and PSA, and thus one would expect that a host with a pre-existing tumor burden would produce more anti-PSA antibodies than a host without tumor burden.

Applicant argues that Example 8 and Figures 10A-B clearly show that mice immunized with AR47.47 produce anti-PSA antibodies that bind to full length PSA and SEQ ID NO:1.

Applicant argues that the Examiner has not provided any factual evidence such as publications as to why the antibodies produced would not bind to SEQ ID NO:1 or circulating prostate specific antigen comprising SEQ ID NO:1. Applicant asserts that thus the Examiner has not met the standards of enablement rejection as set forth in MPEP 2164.

The submission of the Schultes Declaration and the recitation of the references by Chapman et al, Herlyn et al are acknowledged, and entered.

Applicant's arguments in paper No: 30 have been considered but are found not to be persuasive for the following reasons:

Contrary to Applicant's assertion, the Examiner did not state that this application is enabled for a method of treating prostate cancer, comprising administering antibody AR47.47 which specifically binds to the epitope of amino acids 139-163 of PSA in paper No:12. It is noted that in paper No:12, the Examiner statement that this application is enabled for a method of treating prostate cancer, comprising administering antibody

AR47.47 which specifically binds to the epitope of amino acids 139-163 of PSA is from a 112, first paragraph, scope rejection for enablement of a binding agent, wherein said statement is preceded by a requirement that Applicant could overcome the 112, first paragraph, enablement for being not enabled for a method of treating prostate cancer.

It is noted that Ab2 does not bind to PSA, it only binds to Ab1 or AR47.47, and mimics the structure of the antigen epitope or an idiotope of Ab1 that is distinct from the antigen binding site (specification, p.6). Thus detection of Ab2 does not mean that antibodies specific for PSA and anti-anti-idiotypic antibodies are detected.

It is further noted that contrary to Applicant assertion that the claimed invention describes a method that breaks tolerance to self antigen, no Ab3 antibodies, i.e. anti-anti-idiotypic antibodies which recognize the epitope of Ab1, AR47.47 comprising amino acids 139-163 of PSA (SEQ ID NO:1) have been identified in the specification. The assumed Ab3 antibodies are actually antibodies to PSA in mice free of tumor, and which do not have PSA as self antigen (Example 8). The specific epitopes of said assumed Ab3 antibodies are not known, and are called Ab3' antibodies by Applicant in the response, since the specification discloses that in the assay for Ab3 antibodies, the plate is coated with PSA (p.31), and there is no disclosure that the plate is coated with the amino acids 139-163 of PSA.

Concerning Example 11, Applicant argues limitation not in the claims, i.e. the limitation that a subject is pretreated with Ab1 antibody AR47.47 before development of prostate cancer.

Concerning Example 12, the Examiner agrees that it does not exactly represent a model of "treating" human prostate cancer, because the tumor is fast growing compared to mice lifespan. However, concerning a method for producing antibodies against PSA, whether antibodies are produced or not does not depend on the lifespan of mice because antibodies are known in the art to be routinely produced in mice. In Example 12, in all four experiments, 8, 13, 10 and 14, wherein **mice have cancers**, the amount of the putative Ab3 antibodies, which are actually antibodies binding to whole length PSA, and not anti-anti-idiotypic antibodies, are not different between mice treated with Ab1 antibody or AR47.47 and the control mice with tumor burden. Since there is no difference between the control and the treated mice, one would not expect that the putative Ab3 antibodies that bind to the whole length PSA, is produced by Ab1 antibody or AR47.47, nor one would expect that any anti-anti-idiotypic antibody which recognizes the epitope of Ab1, AR47.47, or the amino acids 139-163 of PSA, would be produced by Ab1 antibody.

Further, although the art teaches that Ab3 or anti-anti-idiotypic antibody could be produced from Ab2, which in turn is produced by Ab1 for some antibodies, in some circumstances, Applicant has not shown that for any antibody, Ab1 could always or predictably produce Ab3, and as clearly shown in the specification, no Ab3 actually has been produced that could recognize the epitope of the Ab1 antibody AR47.47 in mice with or without tumor burden.

Concerning Applicant's arguments that cancer patients produce PSA, which allows for immune complex formation between AR47.47 and PSA, and that one would

expect that a host with a pre-existing tumor burden would produce more anti-PSA antibodies than a host without tumor burden, it is noted that this argument is contrary to what has been well known in the art as T-cell anergy, wherein due to the overwhelming presence of antigen, the cytotoxic and proliferative response of tumor-specific T cells are blocked, as taught by Sherman et al and Smith et al, of record. Thus it is unpredictable that proliferative T cells that are needed for B cells activation and producing antibodies would not be anergic in prostate cancer patients. This is clearly shown by example 12 in the specification, wherein in mice with tumor burden antibodies to PSA or the putative Ab3 are not different between the treated animals and the control.

Concerning Example 8 and Figures 10A-B, only mice without tumors are immunized with AR47.47 produce the putative Ab3 antibodies, which are actually anti-PSA antibodies that bind to full length PSA and SEQ ID NO:1. This example would not be applicable to a human patients because different from mice, human patients not only have PSA as self antigen, but also have tumor burden, both of these features would contribute to the suppression of production of anti-PSA antibodies in said patients, via self-tolerance and T cell anergy, as taught by Sherman et al, and Smith et al, of record.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION, NEW REJECTION

The instant specification does not contain a written description of the invention in such full, clear, concise, and exact terms or in sufficient detail that one skilled in the art

can reasonably conclude that applicant had possession of the claimed invention at the time of filing.

Claims 35-36 are rejected under 35 USC 112, first paragraph, as lacking an adequate written description in the specification.

Claims 35-36 are drawn to a method for inducing an immune response to prostate specific antigen, or Ab3 that specifically binds to prostate specific antigen, comprising administering an Ab1, which specifically binds to an epitope of circulating prostate specific antigen, the epitope comprising the sequence of SEQ ID NO:1, wherein the Ab1 is "one member of an immunologic pair".

The specification discloses that a binding agent (BA), as used herein, refers to one member of an immunologic pair, e.g., a binding moiety that is capable of binding to a single epitope expressed on the tumor antigen (p.10, third paragraph). Examples of binding agents include, but are not limited to antibodies, and tumor binding peptides.

The specification does not disclose however the structure of the tumor binding peptides.

It is noted that "one member of an immunologic pair" encompass a genus of binding agents having different structures, besides antibodies that bind to SEQ ID NO:1; for example, tumor binding peptides of any structure, radiolabel compounds, small molecule agonists or antagonists that bind to SEQ ID NO:1, etc...

The instant disclosure of a single species of "one member of an immunologic pair" does not adequately describe the scope of the claimed genus, which encompasses a substantial variety of subgenera.

Although drawn to DNA the following teaching clearly applies to the instant invention. A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the claimed "one member of an immunologic pair". There is no description of the conserved regions which are critical to the structure and function of the genus claimed.

Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of specific "one member of an immunologic pair", antibodies that bind to SEQ ID NO:1, is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Thus, only a method for inducing an immune response to prostate specific antigen, or Ab3 that specifically binds to prostate specific antigen, comprising administering an Ab1, which specifically binds to an epitope of circulating prostate specific antigen, the epitope comprising the sequence of SEQ ID NO:1, wherein the Ab1 is an antibody, monoclonal antibody, a single chain antibody, a humanized antibody,

and a chimeric antibody, or an antigen binding fragment thereof, but not the full breadth of the claims meet the written description provisions of 35 USC 112, first paragraph.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE, NEW REJECTION

1. If Applicant could overcome the above 112, first paragraph rejection, claims 35-36 are still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for inducing an immune response to prostate specific antigen, or Ab3 that specifically binds to prostate specific antigen, comprising administering an Ab1, which specifically binds to an epitope of circulating prostate specific antigen, the epitope comprising the sequence of SEQ ID NO:1, wherein the Ab1 is an antibody, monoclonal antibody, a single chain antibody, a humanized antibody, and a chimeric antibody, or an antigen binding fragment thereof, **does not reasonably provide enablement for** a method for inducing an immune response to prostate specific antigen, or Ab3 that specifically binds to prostate specific antigen, comprising administering an Ab1, which specifically binds to an epitope of circulating prostate specific antigen, the epitope comprising the sequence of SEQ ID NO:1, wherein the Ab1 is **"one member of an immunologic pair".** The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 35-36 are drawn to a method for inducing an immune response to prostate specific antigen, or Ab3 that specifically binds to prostate specific antigen, comprising administering an Ab1, which specifically binds to an epitope of circulating

prostate specific antigen, the epitope comprising the sequence of SEQ ID NO:1, wherein the Ab1 is "one member of an immunologic pair".

The specification discloses that a binding agent (BA), as used herein, refers to one member of an immunologic pair, e.g., a binding moiety that is capable of binding to a single epitope expressed on the tumor antigen (p.10, third paragraph). Examples of binding agents include, but are not limited to antibodies, and tumor binding peptides.

It is noted that "one member of an immunologic pair" encompass a genus of binding agents having different structures, besides antibodies that bind to SEQ ID NO:1; for example, tumor binding peptides of any structure, radiolabel compounds, small molecule agonists or antagonists that bind to SEQ ID NO:1, etc...

The specification does not disclose the structure of myriads of tumor binding peptides, small molecule agonists or antagonists that bind to SEQ ID NO:1, nor how to make such diverse binding agents.

In the absence of a teaching of how to make the claimed "member of an immunologic pair", other than antibodies that bind to SEQ ID NO:1, it would be undue experimentation for one of skill in the art to practice the claimed invention.

2. If Applicant could overcome the above 112, first paragraph rejection, claims 35-36 are still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for inducing an immune response to prostate specific antigen, or Ab3 that specifically binds to prostate specific antigen, comprising administering an Ab1, which specifically binds to an epitope of circulating prostate specific antigen, the epitope comprising the sequence of SEQ ID NO:1, wherein the Ab1

is an antibody, monoclonal antibody, a single chain antibody, a humanized antibody, and a chimeric antibody, or an antigen binding fragment thereof, **does not reasonably provide enablement for** a method for inducing an immune response to prostate specific antigen, or Ab3 that specifically binds to prostate specific antigen, comprising administering an Ab1, which specifically binds to an epitope of circulating prostate specific antigen, the epitope comprising the sequence of SEQ ID NO:1, wherein the Ab1 is **"a fragment of an antibody"**. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 35-36 are drawn to a method for inducing an immune response to prostate specific antigen, or Ab3 that specifically binds to prostate specific antigen, comprising administering an Ab1, which specifically binds to an epitope of circulating prostate specific antigen, the epitope comprising the sequence of SEQ ID NO:1, wherein the Ab1 is a fragment of an antibody.

It is noted that not any fragment of an antibody would bind to the target antigen. Thus the antibody fragment of the claimed method would not necessarily have the properties of the antibodies that specifically bind to SEQ ID NO:1.

The specification does not teach how to induce an immune response to prostate specific antigen, or Ab3 that specifically binds to prostate specific antigen, comprising administering an antibody fragment of Ab1.

In the absence of a teaching of how to induce an immune response to prostate specific antigen, or Ab3 that specifically binds to prostate specific antigen, using any

fragment of Ab1, and in view that the antibody fragment would not necessarily bind to SEQ ID NO:1, one cannot predict that a specific immune response to prostate specific antigen, or Ab3 that specifically binds to prostate specific antigen would be induced.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

It is noted that this rejection could be obviated by amending the claims for example, to recite "an antigen-binding fragment thereof".

REJECTION UNDER 35 USC 102(b), NEW REJECTION

Claims 15, 17, 35, 37 are rejected under 35 USC 102(b) as being anticipated by Meyers et al, 1989, Prostate, 14(3): 209-20.

Claims 15, 17, 35, 37 are drawn to a method for inducing an immune response to prostate specific antigen, comprising administering an Ab1, which specifically binds to an epitope of circulating prostate specific antigen, the epitope "comprising" the sequence of SEQ ID NO:1, the Ab1 being capable of binding to the antigen to form an immunogenic Ab1-antigen complex, wherein the immune response comprises a human and cellular immune response, wherein the Ab1 isa monoclonal antibody, and wherein the Ab1 antibody is a xenogenic antibody.

It is noted that due to the language "comprising", the epitope comprising the sequence of SEQ ID NO:1 encompasses full length prostate specific antigen sequence.

Meyers et al teach injection into ten patients with labeled monoclonal antibody against prostate specific antigen.

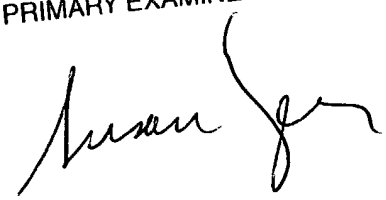
Because the method of the prior art comprises the same method steps as claimed in the instant invention using the same composition, the claimed method is anticipated because the method will inherently lead to the claimed effects. See Ex parte Novitski 26 USPQ 1389 (BPAI 1993).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 703-305-2008. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANTHONY CAPUTA can be reached on 703-308-3995. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

SUSAN UNGAR, PH.D
PRIMARY EXAMINER



MINH TAM DAVIS

December 23, 2003